RA Infection Risk Linked to Comorbidities

BY KATE JOHNSON

QUEBEC CITY — The increased rate of serious infections seen in patients with rheumatoid arthritis is most strongly associated with current glucocorticoid exposure, but comorbidities are also an important factor, according to findings from a large, nested, case-control study presented at the annual meeting of the Canadian Rheumatology Association.

"When we try to predict risk of infection, we tend to focus on the drugs, particularly the immunosuppressive agents," said principal investigator Dr. Claire Bombardier in an interview. The findings from this research show that rheumatologists need to pay more attention to other, heretofore largely overlooked risk factors, she added.

Dr. Bombardier noted her study's serious flaw: It relies on data from a source that does not include complete information on exposure to biologic agents. Use of biologics has been linked to an increased risk for reactivation of tuberculosis as well as primary fungal and other infections.

In two separate posters, Dr. Bombardier presented a retrospective examination of serious infections requiring hospitalization, as well as serious fungal infections, in a cohort of 81,497 seniors with RA.

All subjects were aged older than 65 years (mean, 69 years), and were drawn from the Ontario Biologics Research Initiative administrative database, said Dr. Bombardier, professor of medicine and director of the division of rheumatology at the University of Toronto.

The first study involved a total of 14,214 subjects with serious infection requiring hospitalization in 1992-2006, with the most common infection being pneumonia (n = 7,026). These subjects were matched to controls from the same cohort according to age, sex, and year of cohort entry. Multivariate logistic regression analysis was used to assess the independent effects of demographics (age, income, rural/urban residence); comorbidity (based on the Charlson-Deyo comorbidity index); markers of RA severity (number of rheumatology visits, history of joint replacement, presence of extra-articular RA, and prescription NSAID use); and RA-related drug exposure. Past and current drug exposures were determined based on electronic provincial prescription data, although most biologic use was probably not captured in this database because it is not covered by provincial health insurance.

After adjustment, the study found that current use of glucocorticoids was associated with the highest risk of infection, and that this risk increased with increasing doses. Compared with no exposure, a glucocorticoid dose of 5 mg or less per day was associated with an odds ratio of infection of 3.81. At 6-9 mg/day, the OR was 4.56, rising to 5.58 at a dose of 10-19 mg/day, and the OR was 5.46 at a dose of 20 mg or more per day.

But other drugs—both biologics (to the extent their effect was assessed) and disease-modifying antirheumatic drugs—were also associated with risk, although less so, with ORs ranging from 1.1 to 3.64, said Dr. Bombardier. Within the context of these nonglucocorticoid drugs, comorbidity and markers of disease severity were associated with a similar range of risks of infection. Chronic lung disease was associated with an OR of 1.47, and renal disease with OR of 1.38. The Charlson-Deyo comorbidity index score of 1 had an OR of 1.44, whereas a score of 2 or more had an OR of 1.59.

In terms of markers of disease activity, the presence of one or more extra-articular feature of RA was associated with an OR of 1.14, and a history of joint replacement with an OR of 1.05.

Dr. Bombardier's second study focused specifically on the risk of serious fungal infections within the same cohort, because of "the flurry of interest in fungal infections recently," she said.

A total of 53 serious fungal infections occurred within the cohort, including aspergillosis, coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, and systemic candidiasis. As with the previous study, cases of infection were matched to 265 controls from the same cohort.

Again, univariate and multivariate logistic regression analysis assessed the independent effects of demographics, comorbidity, markers of RA severity, and RA-related drug exposure.

After adjustment, the study found that cases were more likely than controls to live in rural areas (OR, 6.8) and to have more comorbidity, most commonly lung (OR, 1.27) and renal disease (OR, 1.95).

Compared with no prednisone, there was a greater risk of fungal infection associated with prednisone doses of 10-19 mg/day (OR, 1.90) and more than 20 mg/day (OR, 4.0).

Only 17 of 53 cases were currently exposed to a DMARD at the time of the fungal infection, and no case was currently exposed to a biologic agent.

Compared with no exposure, a higher risk of infection was associated with current exposure to sulfasalazine (OR, 1.90), methotrexate (OR, 1.66), and hydroxychloroquine (OR, 1.64).

Dr. Bombardier said this information should help physicians refine decision making about adjusting RA patients' medication dose.

"When you're worrying about a patient, don't focus just on the drugs. Think about whether they have renal disease, or whether they have lung disease. That is as important [as], if not more important than, worrying about the drugs," she said. ■

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Two Biomarkers May Predict Rituximab Response in RA

BY KATE JOHNSON

QUEBEC CITY — Baseline serologic biomarkers offer rheumatologists the possibility of tailoring rheumatoid arthritis medications to fit various subgroups of patients, thereby increasing the likelihood of achieving a good response to treatment, said Dr. Rafat Faraawi at the annual meeting of the Canadian Rheumatology Association.

In a sea of pharmaceuticals for RA, with no clear understanding of why some patients respond to one agent and not to another, biomarkers are a potential tool for predicting treatment response, Dr. Faraawi said in an interview with RHEUMATOLOGY NEWS.

"We still don't have guidelines on how to select pharmaceuticals. More or less, [the drugs] all have the same efficacy. There are minor differences, and then the selection depends on many factors.

"We depend on personal preference, physician experience, certain peculiarities of the drugs, mechanism of action," according to Dr. Faraawi.

In a post hoc analysis of two large trials of rituximab, his group discovered that a subgroup of patients with high serum levels of C-reactive protein (CRP) as well as seropositivity for rheumatoid factor (RF) had the highest response to rituximab. "If you want to select patients who will get a response to this expensive biologic, then those with positive rheumatoid factor and an elevated C-reactive protein most likely will show a better response than [will] seronegative patients or those with low CRP.

"And if they have a combination of both, that is even better," said Dr. Faraawi, who is a rheumatologist at McMaster University in Kitchener, Ont.

He presented the data as a poster at the meeting.

The investigators used data from REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) and SERENE (Study Evaluating Rituximab's Efficacy in Methotrexate Inadequate Responders).

Both are randomized, placebo-controlled trials of rituximab in patients with inadequate response to either tumor necrosis factor inhibitors or methotrexate, respectively (Arthritis Rheum. 2006;54:2793-806; ACR 2008, abstract 364).

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Major Finding: Response rate to rituximab is highest in RA patients with elevated CRP and RF positivity.

Data Source: Post hoc analysis of data from REFLEX and SERENE trials.

Disclosures: The study was supported by Genentech Inc., F. Hoffmann-LaRoche Ltd., and Biogen Idec Inc. Dr. Faraawi reported receiving research grants from Roche, Pfizer Inc., UCB, Schering-Plough Corp., and Wyeth.

Both trials reported ACR 50 response rates for rituximab, compared with placebo, after 24 weeks.

The REFLEX trial (n = 517) showed an ACR 50 response of 27% in the treated group, compared with 5% in placebo. And the SERENE trial (n = 501) showed an ACR 50 response of 26% in the treated group, compared with 9% in placebo.

For both trials, baseline levels of 19 serologic markers and 9 clinical features were recorded.

After an analysis of baseline and outcome data from both trials, Dr. Faraawi's study identified four serologic biomarkers—RF, CRP, IgG anti–cyclic citrullinated peptide 3 (CCP3) antibodies, and soluble cluster of differentiation 25 (CD25)—that were predictive of response to rituximab, he explained.

Of these, seropositivity for RF and CRP were the most predictive, and this was further enhanced when both biomarkers were presented.

For example, in the REFLEX trial, the overall ACR 50 response rate was 27% in the treated group, whereas the subgroup of patients with CRP levels above 2.9 mg/dL and positive RF of any isotope (defined as IgA RF greater than 25 U/mL, IgG RF greater than 20 U/mL, IgM RF greater than 20 U/mL, total RF greater than 20 IU/mL) had an ACR 50 response rate of 31% (placebo, 1%).

Similarly, in the SERENE trial, the overall ACR 50 response rate was 26% in the treated group, whereas the response rate was 39% in the same subgroup of patients who were positive for RF and had an elevated CRP (placebo, 7%).

Rituximab is a monoclonal antibody that selectively targets CD20-positive B cells, which secrete rheumatoid factor, said Dr. Faraawi.

"That is why, for this particular drug, patients with positive rheumatoid factor respond well. That doesn't mean this agent does not work for patients with low markers. It still works. But the likelihood of response is greater with positive markers."

He said that large trials are needed to further clarify which markers can help in the selection of agents for specific patients. ■